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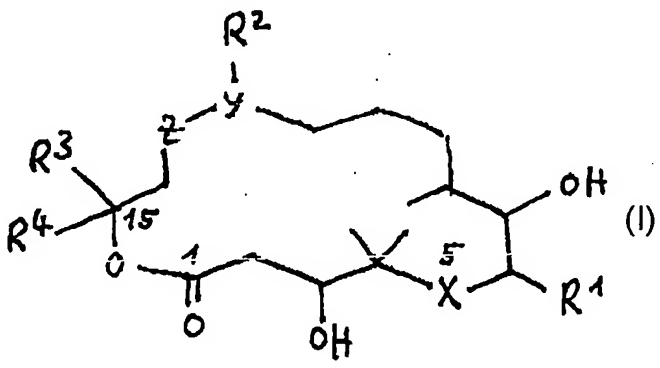
(54) Title: GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF)



(I)

(57) Abstract: The invention relates to 5-thiapethilones and 15-disubstituted epothilones according to formula I (I) with the following meanings: X= >C = O or >S = O R^1 = C_{1-6} alkyl or C_{2-6} alkenyl R^2 = H or C_{1-6} alkyl Y - Z = >C=C< or >C-O-C< (epoxide ring) R^3 = H, C_{1-6} alkyl or C_{2-6} alkenyl R^4= bicycloaryl, bicycloheteroaryl or -C(R^5) = CH-R^6, where R^5 = H or CH_3 and R^6 = aryl or heteroaryl X not being >C=O if R^3 = H.

Gesellschaft für Biotechnologische Forschung mbH (GBF)

5-THIAEPOTHILONES AND 15-DISUBSTITUTED EPOTHILONES

The present invention relates to 5-thiaepothilones and 15-disubstituted epothilones which are 16-membered cytotoxic macrolides of formula I with an application potential in cancer therapy and in the treatment of other instances of cell growth impairment.

Epothilones are well known. They can be obtained by fermenting the myxobacterium Sorangium cellulosum (GBF) by semisynthesis (GBF, BMS) by genetic engineering and heterologous expression (Kosan Biosciences), by total synthesis (Danishefsky, Nicolaou, Schinzer, Novartis, Schering).

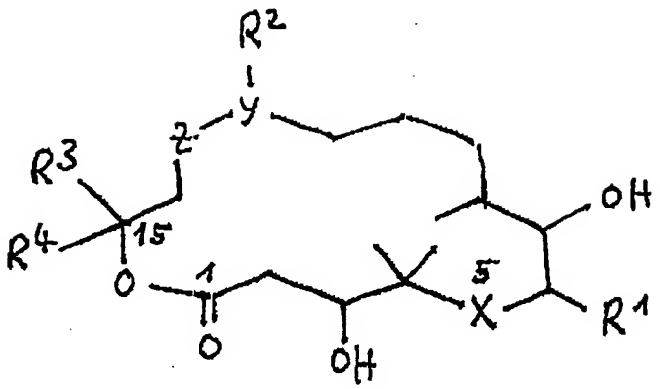
All the epothilones which have become known so far have the common characteristic of carrying a keto group (X = carbonyl) in position 5 and a hydrogen (R^3 = H) on the C15 atom. The present invention relates to epothilones which, in contrast to the known state of the art, exhibit either

(1) a sulphoxide group for X or

(2) an alkyl or alkenyl group by way of R^3 on the C15 carbon atom or

(3) both a sulphoxide group X and an alkyl or alkenyl group as radical R^3.

The invention also relates to epothilones of the following general formula I:



I

with the following meanings:

X = >C = O or >S = O
R^1 = C_{1-6} alkyl or C_{2-6} alkenyl
R^2 = H or C_{1-6} alkyl
Y - Z = >C=C< or >C-O-C< (epoxide ring)
R^3 = H, C_{1-6} alkyl or C_{2-6} alkenyl
R^4 = bicycloaryl, bicycloheteroaryl or $-C(R^5) = CH-R^6$,

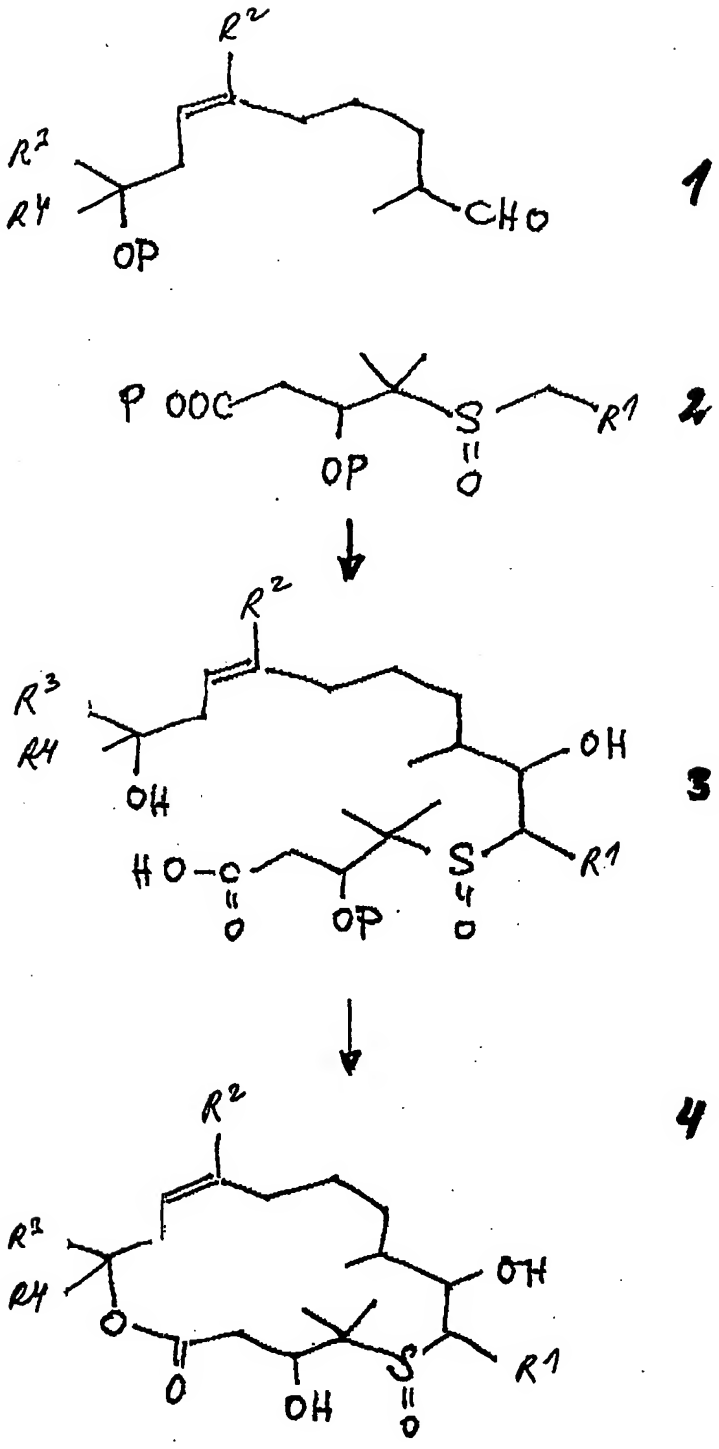
where

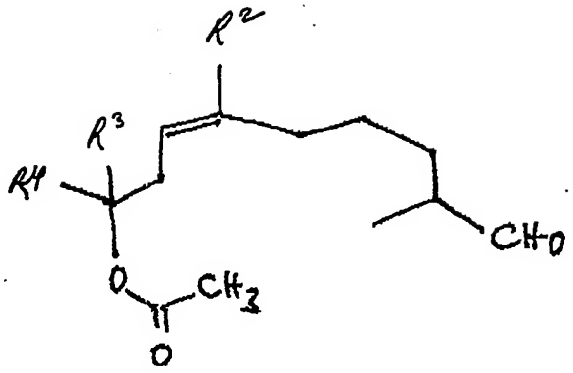
R^5 = H or CH_3 and
R^6 = aryl or heteroaryl
X not being >C=O if R^3 = H.

A compound of the general formula I with Z-Y = >C=C< can be produced from a compound of formula 1 by aldol reaction with a compound of formula 2. In the following reaction scheme, P represents a protective group common in epothilone chemistry, such as a silyl group. Subsequently, the compound of formula 3 thus obtained is reacted, with ring closure (formation of lactone), to a compound of formula 4.

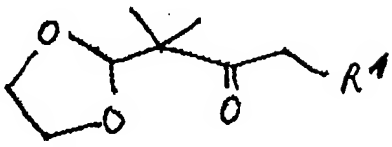
A compound of the general formula I with Y-Z = >C-O-C< (epoxide ring) can be produced by reacting a compound of formula 5 with a compound of formula 6 in an aldol

reaction. The resulting compound of formula 7 can be cyclised after liberating the aldehyde group from the acetal in an aldol reaction, whereupon the lactone thus obtained is subjected to epoxidation in position 12,13.

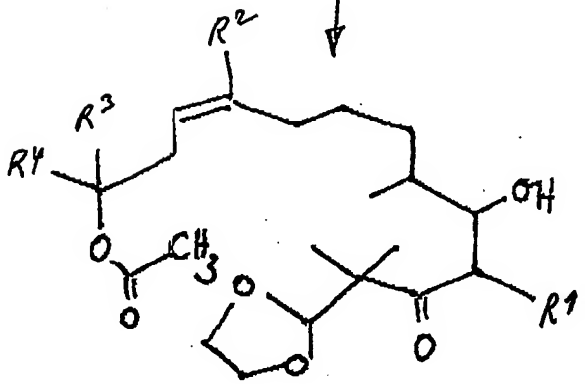

R2
R3
R4
OP
CHO
1
P OOC
S
R1
2
OP
O
R3
OH
3
HO-C
4
4


R2
R3
R4
CHO
O
CH3
O

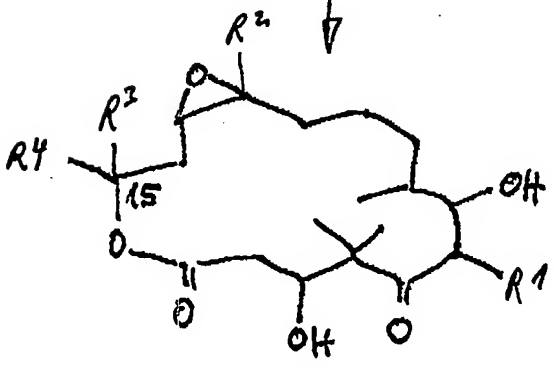
5


O
O
O
R1

6


R2
R3
R4
OH
O
CH3
O
O
O
R1

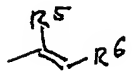
7


R2
R3
R4
15
O
OH
O
O
OH
R1

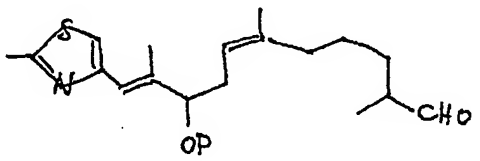
8

Below, the invention is further illustrated by two synthesis examples.

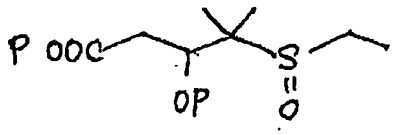
Synthesis example Ia: X = SO, R^1, R^2 = CH_3,

Z - Y = C=C, R^3 = H, R^4 = 

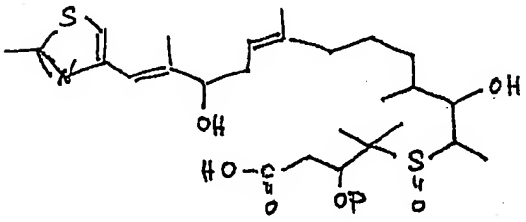
with R^5 = CH_3 , R^6 = 4-(2-methylthiazolyl)

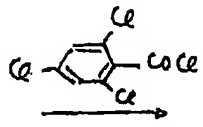


$(Me_3Si)_2NLi$ →



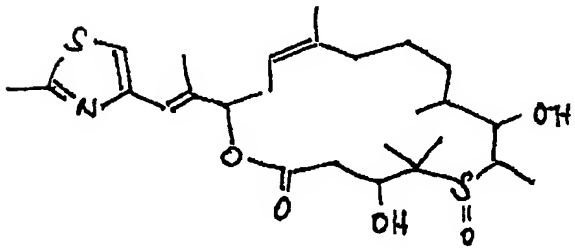
P = protective groups, e.g. silyl





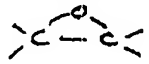
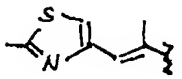
HF →

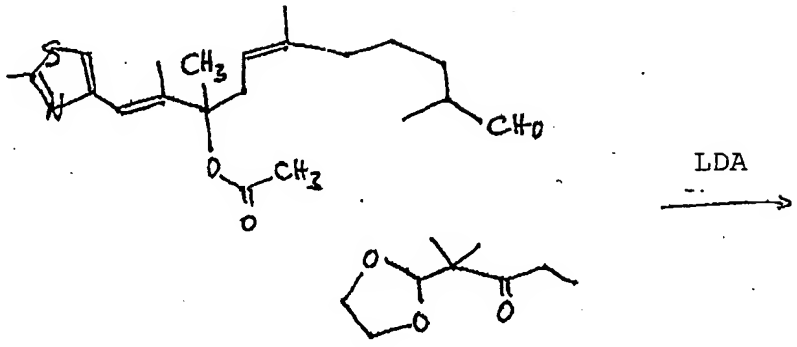
Net_3, DMAP, pyiridine

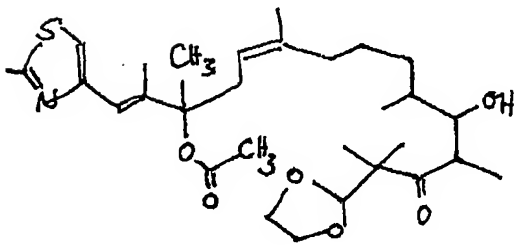


5-thiaepothilone

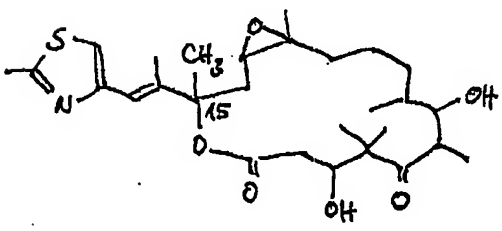
Synthesis example Ib: X = C = O, R^1, R^2 = CH_3,

Z - Y =  R^3 = CO_3, R^4 = 





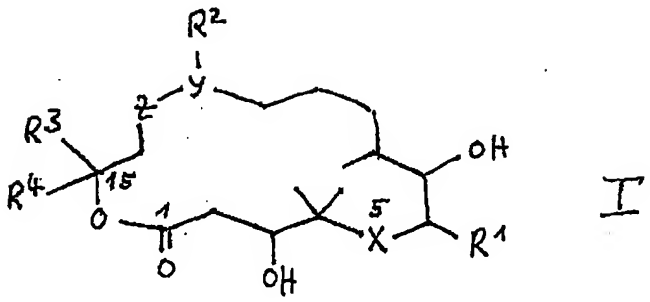
1. Cerium-ammonium nitrate
2.+ BnLi
3. Dimethyl dioxirane



= 15-Methyl epothilone B

CLAIMS

1. Epothilone of the general formula (I):



I

with the following meanings:

X = >C = O or >S = O and/or
R^1 = C_{1-6} alkyl or C_{2-6} alkenyl and/or
R^2 = H or C_{1-6} alkyl and/or
Y - Z = >C=C< or >C-O-C< (epoxide ring) and/or
R^3 = H, C_{1-6} alkyl or C_{2-6} alkenyl and/or
R^4 = bicycloaryl, bicycloheteroaryl or $-C(R^5) = CH-R^6$,

where

R^5 = H or CH_3 and
R^6 = aryl or heteroaryl,
X not being >C=O if R^3 = H,

and one, a plurality or all conceivable combinations of the radicals X, R^1, R^2, R^3, R^4, R^5, R^6 and Y - Z

2. Epothilone according to claim 1, where R^4 is a bicycloaryl or bicycloheteroaryl radical common in epothilone chemistry.

3. Epothilone according to claim 1, where R^6 is an aryl or heteroaryl radical common in epothilone chemistry.

4. Epothilone according to claim 3, where the heteroaryl radical is a monocyclic 5 or 6-membered heteroaromatic which may exhibit one or a plurality of O and/or N and/or S atoms in the ring.

5. Epothilone according to claim 3, where the aryl radical may be a heteroaromatic with one or a plurality of and in particular 1, 2, 3 or 4 heteroatoms.

6. Agent for cancer therapy and/or treating other instances of cell growth impairment, consisting of or containing one or a plurality of epothilones according to any one of the preceding claims, apart from the usual auxiliary agents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D313/00 C07D327/02 C07D417/06 C07D497/04 C07D493/04
A61K31/425 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02514 A (BRISTOL-MYERS) 21 January 1999 (1999-01-21) page 64; claims 1,3-5	1,3,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2003	14/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06066

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